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Stem Cell Research: Science, Federal Research Funding, and Regulatory Oversight

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Summary

Since FY1996, the Dickey amendment in Labor-Health and Human Services (HHS) appropriations acts has prohibited the use of federal funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. At the time, the Dickey amendment halted the development of guidelines by the National Institutes of Health (NIH) on the broad field of human embryo research and has each year since 1996 prohibited federal funding for human embryo research and related topics, including in vitro fertilization (IVF) and human embryonic stem cells. These cells have the ability to develop into virtually any cell in the body, and may have the potential to treat injuries as well as illnesses, such as diabetes and Parkinson's disease. Currently, most human embryonic stem cell lines used in research are derived from embryos produced via IVF. Because the process of removing these cells destroys the embryo, some individuals believe the derivation of stem cells from human embryos is ethically unacceptable.

In August 2001, President George W. Bush announced that for the first time, federal funds would be used to support research on human embryonic stem cells. However, the Bush decision limited funding to research on 21 stem cell lines that had been created prior to the date of the August 2001 policy announcement. Scientists expressed concern about the quality and longevity of these 21 stem cell lines, believing that research advancement requires access to new human embryonic stem cell lines. However, those concerned about the ethical implications of deriving stem cells from human embryos argue that researchers should use alternatives, such as induced pluripotent stem (iPS) cells or adult stem cells (from bone marrow or umbilical cord blood). In June 2007, President Bush signed an executive order directing the support of "research on the isolation, derivation, production and testing of stem cells that are capable of producing all or almost all of the cell types of the developing body and may result in improved understanding of or treatments for diseases and other adverse health conditions, but are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus." Many scientists continued to stress that research should focus on all types of stem cells, including those derived from human embryos.

On March 9, 2009, President Barack Obama signed an executive order that reversed the nearly eight-year-old Bush Administration restriction on federal funding for human embryonic stem cell research and the June 2007 executive order. The Obama decision directed NIH to issue new guidelines for the conduct of embryonic stem cell research. Draft guidelines were released on April 23, 2009, and final guidelines were issued on July 6, 2009. In December 2009, NIH created a new registry of human embryonic stem cell lines that are eligible for use in research supported by federal funds under the 2009 guidelines. Shortly after the 2009 guidelines were issued, opponents of human embryonic stem cell research brought suit in federal court arguing that federal funding of such research was barred by the Dickey amendment. Specifically, the litigation turned on whether HHS could lawfully interpret the term "research" to include only activities performed once human embryonic stem cells had been isolated, or whether "research" must also include the antecedent embryonic stem cell derivation activities that generally resulted in the destruction of human embryos. Although federal funding of embryonic stem cell research was briefly enjoined, the United States Court of Appeals for the D.C. Circuit rejected that argument and allowed federal funding of human embryonic stem cell research to continue under the 2009 guidelines. The Supreme Court has declined to review that decision, letting the D.C. Circuit's opinion stand. As of January 8, 2013, a total of 200 stem cell lines are listed in the NIH registry.

Legislation introduced but not passed in the 111th and 112th Congresses would have codified the Obama stem cell policy, preventing reversal by future Administrations. However, even if such

legislation had been enacted, the use of federal funds for the derivation of new human embryonic stem cell lines would still not be permitted as long as the Dickey Amendment remains in effect.

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Introduction

On March 9, 2009, President Barack Obama signed Executive Order 13505, "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells."[1] The Obama executive order permits the Secretary of HHS through NIH to "support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law" and directed NIH to review existing guidelines and "issue new NIH guidance on such research" within 120 days of the date of the executive order.

The Obama decision allows scientists to use federal funds for research using the many human embryonic stem cell lines that have been created since the Bush 2001 policy. The Obama policy also eliminates the need to separate federally funded research from research conducted with private funds on cell lines that were previously ineligible for federal funding under the Bush policy; this often required building new but duplicative laboratories under the Bush policy using funds that could have been spent on associated research.

Draft NIH guidelines were released on April 23, 2009.[2] Final guidelines were issued on July 6, 2009.[3] The Obama decision allows scientists to use federal funds for research on stem cell lines "that are posted on the new NIH Registry or they may establish eligibility by submitting an assurance of compliance" with the July 2009 guidelines.[4] President Obama also issued a memorandum on scientific integrity directing the head of the White House Office of Science and Technology Policy "to develop a strategy for restoring scientific integrity to government decision making."[5]

Shortly after the 2009 guidelines were issued, opponents of human embryonic stem cell research brought suit in federal court arguing that federal funding of such research was barred by the Dickey amendment. [6] Although federal funding of embryonic stem cell research was briefly enjoined by a preliminary injunction between August 23 and September 9, 2010,[7] the United States Court of Appeals for the D.C. Circuit ultimately rejected that argument and allowed federal

[1] "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," March 9, 2009, at http://www.whitehouse.gov/the_press_office/Removing-Barriers-to-Responsible-Scientific-Research-Involving-Human-Stem-Cells/.

[2] Department of Health and Human Services, National Institutes of Health, "Draft National Institutes of Health Guidelines for Human Stem Cell Research Notice," 74 *Federal Register* 18578-18580, April 23, 2009.

[3] Department of Health and Human Services, National Institutes of Health, "National Institutes of Health Guidelines for Human Stem Cell Research," 74 *Federal Register* 32170-32175, July 7, 2009.

[4] Ibid., p. 32174.

[5] The White House, Office of the Press Secretary, Remarks of President Barack Obama-As Prepared for Delivery, Signing of Stem Cell Executive Order and Scientific Integrity Presidential Memorandum, March 9, 2009, at http://www.whitehouse.gov/the_press_office/Remarks-of-the-President-As-Prepared-for-Delivery-Signing-of-Stem-Cell-Executive-Order-and-Scientific-Integrity-Presidential-Memorandum/.

[6] The suit had initially been dismissed for lack of standing. Sherley v. Sebelius, 686 F. Supp. 2d 1 (D.D.C. 2009). However, the case was reinstated after an appellate court ruled that two adult stem cell researchers had sufficiently alleged that they would suffer increased competition for NIH grants if more embryonic stem cell lines were made eligible for federal funds. Sherley v. Sebelius, 610 F.3d 69 (D.C. Cir. 2010).

[7] Sherley v. Sebelius, Civ. No. 1:09-cv-1575 RCL (D.D.C. August 23, 2010) (granting preliminary injunction barring HHS from "implementing, applying, or taking any action whatsoever pursuant to" the NIH 2009 Guidelines "or otherwise funding research involving human embryonic stem cells as contemplated in the Guidelines"); Sherley v. Sebelius, No. 10-5287 (D.C. Cir. September 9, 2010) (granting emergency administrative stay of preliminary injunction).

funding of human embryonic stem cell research to continue under the 2009 guidelines.[8] On January 7, 2013, the Supreme Court denied the plaintiffs' petition for review and let the D.C. Circuit's opinion stand.[9]

The Obama executive order revoked the Bush Administration presidential statement of August 9, 2001, limiting federal funding for research involving human embryonic stem cells, and Executive Order 13435 of June 20, 2007, "which supplements the August 9, 2001, statement on human embryonic stem cell research."[10] President George W. Bush had announced on August 9, 2001, that for the first time federal funds would be used to support research on human embryonic stem cells. However, the Bush decision limited funding to research on 21 stem cell lines that had been created prior to the date of the August 2001 policy announcement. In contrast, as of January 8, 2013, a total of 200 stem cell lines are listed in the new NIH stem cell registry.[11]

Legislation introduced but not passed in the 111th and 112th Congresses would have codified the Obama stem cell policy, preventing reversal by future Administrations.[12] However, even if such legislation had been enacted, the use of federal funds for the derivation of new human embryonic stem cell lines would still not be permitted as long as the Dickey Amendment remains in effect. The amendment states federal funds cannot be used for the creation of human embryos for research purposes or for research in which human embryos are destroyed.

This report provides background information on stem cell research and its potential applications as well as a history of federal policy decisions related to research on human embryos and stem cells.

Basic Research and Potential Applications

Most cells within an animal or human being are committed to fulfilling a single function within the body. In contrast, stem cells are a unique and important set of cells that are not specialized. Stem cells retain the ability to become some of the more than 200 different cell types in the body, and thereby play a critical role in repairing organs and body tissues throughout life. The term *stem cells* is often used in reference to these repair cells within an adult organism, but a more fundamental variety of stem cells is found in the early-stage embryo. Embryonic stem cells have the ability to become all the different types of cells found in the human body. This section discusses background, history, and potential applications of stem cell research.

[8] Sherley v. Sebelius, 644 F.3d 388 (D.C. Cir. 2011) (vacating preliminary injunction). Following the D.C. Circuit's decision, the district court also dismissed the plaintiffs' alternative claim which argued that providing federal funding for human embryonic stem cell research encouraged the derivation of new embryonic stem cells, thereby subjecting human embryos to an increased risk of destruction. Sherley v. Sebelius, 776 F. Supp. 2d 1 (D.D.C. 2011), *aff'd*, 689 F.3d 776 (D.C. Cir. 2012), *cert. denied* 81 U.S.L.W. 3221 (2013).

[9] Sherley v. Sebelius, 81 U.S.L.W. 3221 (2013).

[10] "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," March 9, 2009, at http://www.whitehouse.gov/the_press_office/Removing-Barriers-to-Responsible-Scientific-Research-Involving-Human-Stem-Cells/.

[11] See http://grants.nih.gov/stem_cells/registry/current.htm.

[12] Examples include H.R. 2376 from the 112th Congress and H.R. 872, H.R. 873, S. 487, and H.R. 4808 from the 111th Congress. Such legislation was twice vetoed by President George W. Bush during the 109th and 110th Congresses. See also Alex Wayne, "With Obama Reversal of Stem Cell Policy, Democrats Look to Expand Funding," *CQ Today*, March 9, 2009.

Embryonic Stem Cells from IVF Embryos or Fetal Tissue

Embryonic stem cells were first isolated from mouse embryos in 1981 and from primate embryos in 1995. Animal embryos were the only source for research on embryonic stem cells until November 1998, when two groups of U.S. scientists announced the successful isolation of human embryonic stem cells. One group, at the University of Wisconsin, derived stem cells from five-day-old embryos produced via *in vitro* fertilization (IVF).[13] The second group, at Johns Hopkins University, derived stem cells with very similar properties from five- to nine-week-old embryos or from fetuses obtained through elective abortion.[14]

Both groups reported the human embryos or fetuses were donated for research following a process of informing one or more parents and obtaining their consent. The cells removed from embryos or fetuses were manipulated in the laboratory to create embryonic stem cell lines that may continue to divide for many months to years. The vast majority of research on human embryonic stem cells, both in the United States and overseas, utilizes cell lines derived via the University of Wisconsin method.

Many religious and socially conservative individuals who are opposed to abortion are also opposed to research involving embryos. For these individuals, research involving human embryonic stem cells is of concern because the stem cells are located inside the embryo, and the process of removing the cells destroys the embryo.[15] They believe the destruction of embryos for the purpose of harvesting embryonic stem cells is morally and ethically unacceptable and argue that researchers should use other alternatives, such as induced pluripotent stem (iPS) cells or adult stem cells, both described below, instead of embryonic stem cells.

Induced Pluripotent Stem (iPS) Cells

In 2006, Shinya Yamanaka and his colleagues at Kyoto University in Japan published a paper showing that the addition of four mouse genes into mouse skin cell lines could cause some of the cells to behave like embryonic stem cells. Earlier studies in mouse embryos by Yamanaka's group had identified genes that are active in early embryos; combinations of these genes were then used to try and reprogram adult mouse cells to act like embryonic stem cells. Until this development—called induced pluripotent stem (iPS) cells—the characteristics displayed by the iPS cells were thought to occur only in cells found within the embryo. In 2012, Shinya Yamanaka was awarded the Nobel Prize in Physiology or Medicine for this work.[16]

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[13] The IVF embryos were originally created for the treatment of infertility. Excess embryos are often frozen for future use. A couple may elect to discard their excess embryos, donate the embryos for research, or allow another couple to adopt an embryo. The Society for Assisted Reproductive Technology and RAND conducted a survey of more than 430 infertility clinics to determine the number of frozen embryos in the United States; 340 clinics responded to the survey. Nearly 400,000 embryos have been frozen and stored since the late 1970s. The vast majority of embryos are being held to help couples have children at a later date. Patients have designated 2.8%, or about 11,000 embryos, for research. Scientists estimate these 11,000 could form up to 275 stem cell lines (perhaps much less). http://www.rand.org/pubs/research_briefs/RB9038/index1.html.

[14] Scientists and physicians use the term "embryo" for the first eight weeks after fertilization, and "fetus" for the ninth week through birth. In contrast, HHS regulations define "fetus" as "the product of conception from the time of implantation." (45 C.F.R. §46.203).

[15] For further information, see CRS Report RL33554, *Stem Cell Research: Ethical and Legal Issues*, by Erin D. Williams, Edward C. Liu, and Judith A. Johnson.

[16] The 2012 prize was jointly awarded to Yamanaka and John Gurdon, who, while working at the University of Oxford in the early 1960s, showed that the nucleus of a mature cell (tadpole intestine) could be reprogramed by a (frog) egg cell, the first demonstration of cloning. Gretchen Vogel and Dennis Normile, "Reprogrammed cells earn biologists top

In November 2007, Yamanaka's group, and a second at the University of Wisconsin, announced a similar development in human cells through the introduction of four genes into human skin cells.[17] The research teams accomplished the reprogramming of the adult skin cells by using a retrovirus to transport the four genes into the skin cells. The two teams each used a different set of four genes; the Kyoto group has subsequently achieved reprogramming using three genes.[18]

Some who are opposed to human embryonic stem cell research argue that "scientific reasons alone will now incline even the most willful researchers to leave the human embryo alone.… [The iPS technique] is so simple and powerful. The embryonic stem cell debate is over."[19] Others, however, argue that although development of iPS cells may one day lessen the need to study stem cells derived from the human embryo, "it would be premature" to stop working with human embryonic stem cells for several reasons.[20] For example, it is unclear whether iPS cells share all the characteristics of embryonic stem cells, and therefore multiple comparisons between the two types of cells will be necessary. In addition, because scientists have used potentially cancer-causing retroviruses to transfer the reprogramming genes, these iPS cells would not be desirable for therapeutic uses in patients. Therefore, alternative mechanisms to accomplish reprogramming would need to be developed. Scientists are in the process of investigating the use of other safer viruses to transfer the genes. Some groups are exploring chemical methods of achieving the same results by switching on genes in the adult cell rather than transferring in additional gene copies with a virus.

Embryonic Stem Cells Obtained via SCNT (Cloning)

Another potential source of embryonic stem cells is somatic cell nuclear transfer (SCNT), also referred to as *cloning*.[21] In SCNT the nucleus of an egg is removed and replaced by the nucleus from a mature body cell, such as a skin cell obtained from a patient. In 1996, scientists in Scotland used the SCNT procedure to produce Dolly the sheep, the first mammalian clone.[22] When SCNT is used to create another individual, such as Dolly, the process is called reproductive cloning. In contrast, scientists interested in using SCNT to create cloned stem cells would allow the cell created via SCNT to develop for a few days, and then the stem cells would be removed for research. Creating stem cells using SCNT for research purposes is sometimes referred to as *therapeutic cloning*. Stem cells created via SCNT would be genetically identical to the patient, and thus would avoid any tissue rejection problems that could occur if the cells were transplanted into the patient.

Although various scientific groups have reported success in using SCNT to create cloned embryos (which are then used to produce stem cell lines or live births) of a variety of different

honor," *Science*, vol. 338 (October 12, 2012), pp. 178-179.

[17] Gretchen Vogel and Constance Holden, "Field Leaps Forward with New Stem Cell Advances," *Science*, v. 318, November 23, 2007, pp. 1224-1225.

[18] Dennis Normile, "Shinya Yamanaka: Modest Researcher, Results to Brag About," *Science*, v. 319, February 1, 2008, p. 562.

[19] Charles Krauthammer, "Stem cell vindication," *The Washington Post*, November 30, 2007.

[20] Constance Holden and Gretchen Vogel, "A Seismic Shift for Stem Cell Research," *Science*, v. 319, February 1, 2008, pp. 560-563.

[21] A somatic cell is a body cell. In contrast, a germ cell is an egg or sperm cell.

[22] Dolly was euthanized in February 2003 after developing a lung infection. Some claim her death at six years was related to being a clone, but her ailment may also have occurred because she was raised indoors (for security reasons) rather than as a pastured sheep, which often live to 12 years of age. G. Kolata, "First Mammal Clone Dies," *New York Times*, February 15, 2003, p. A4.

mammals (sheep, rabbits, cows), attempts at creating primate embryos via SCNT had been unsuccessful. However, in June 2007, researchers at the Oregon National Primate Research Center at Oregon Health and Science University announced the successful derivation of stem cells from a rhesus monkey embryo created via SCNT.[23] Results of the Oregon group were confirmed in November 2007.[24]

The unsubstantiated announcement by Clonaid in December 2002 of the birth of a cloned child contributed to the controversy over research on human embryos.[25] In addition, charges of ethical and scientific misconduct clouded the reputation of scientists involved in deriving stem cells from human embryos created via SCNT. In February 2004, scientists at the Seoul National University (SNU) in South Korea announced the first isolation of stem cells from a cloned human embryo and in May 2005 announced advances in the efficiency of creating cloned human embryos and in isolating human stem cells. Concerns about the SNU work arose in November 2005 when a U.S. co-author of the 2005 paper accused Hwang Woo Suk, the lead SNU researcher, of ethical misconduct.[26] In December 2005, a Korean co-author of the May 2005 paper stated that the research was fabricated and the paper should be retracted; Hwang agreed to the retraction. On January 10, 2006, SNU stated that results of the 2004 paper were also a deliberate fabrication.[27]

Stem Cells from Adult Tissue or Umbilical Cord Blood

Stem cells obtained from adult organisms are also the focus of research. Such work is evaluating the characteristics of adult stem cells from a variety of different sources, such as bone marrow and the umbilical cord following birth. Bone marrow transplantation, a type of adult stem cell therapy, has been used for 50 years to treat patients for a variety of blood-related conditions.[28] Bone marrow is one source of hematopoietic stem cells—cells that have the capacity to multiply and differentiate into all types of blood cells. Umbilical cord blood is another source of hematopoietic stem cells.

Opponents of stem cell research advocate that adult instead of embryonic stem cell research should be pursued because they believe the derivation of stem cells from IVF embryos is ethically unacceptable. Others believe that adult stem cells should not be the sole target of research because of important scientific and technical limitations. Adult stem cells may not be as long lived or capable of as many cell divisions as embryonic stem cells. Also, adult stem cells may not be as versatile in developing into various types of tissue as embryonic stem cells, and the location and rarity of the cells in the body might rule out safe and easy access. For these reasons, many scientists argue that both adult and embryonic stem cells should be the subject of research, allowing for a comparison of their various capabilities. Reports issued by the NIH and the Institute of Medicine (IOM) state that both embryonic and adult stem cell research should be pursued.[29]

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[23] Elizabeth Finkel, "Researchers Derive Stem Cells From Monkeys," *ScienceNOW Daily News*, June 19, 2007.

[24] Vogel and Holden, "Field Leaps Forward with New Stem Cell Advances," p. 1224.

[25] For further information, see CRS Report RL31358, *Human Cloning*, by Judith A. Johnson and Erin D. Williams.

[26] Gretchen Vogel, "Collaborators Split over Ethics Allegations" *Science*, November 18, 2005, p. 1100.

[27] Nicholas Wade and Choe Sang-Hun, "Researcher Faked Evidence of Human Cloning, Koreans Report," *The New York Times*, January 10, 2006, p. A1.

[28] Frederick R. Appelbaum, "Hematopoietic-Cell Transplantation at 50," *The New England Journal of Medicine*, v. 357, October 11, 2007, pp. 1472-1475.

[29] National Institutes of Health, Department of Health and Human Services, *Stem Cells: Scientific Progress and Future Research Directions*, June 2001, available at http://stemcells.nih.gov/info/scireport/. Institute of Medicine, *Stem Cells and the Future of Regenerative Medicine*, 2002, available at http://www.nas.edu.

In FY2004, the Consolidated Appropriations Act, 2004 (P.L. 108-199), provided $10 million to establish a National Cord Blood Stem Cell Bank within the Health Resources and Services Administration (HRSA). HRSA was directed to use $1 million to contract with the IOM to conduct a study that would recommend an optimal structure for the program. The study, *Cord Blood: Establishing a National Hematopoietic Stem Cell Bank Program*, was released in April 2005. As stated above, the blood cell forming (hematopoietic) stem cells found in cord blood can be used as an alternative to bone marrow transplantation in the treatment of leukemia, lymphoma, certain types of anemia, and inherited disorders of immunity and metabolism. The IOM report provides the logistical process for establishing a national cord blood banking system, establishes uniform standards for cord blood collection and storage, and provides recommendations on ethical and legal issues associated with cord blood collection, storage and use.

On December 20, 2005, President George W. Bush signed the Stem Cell Therapeutic and Research Act of 2005 (P.L. 109-129). The act provided for the collection and maintenance of human cord blood for the treatment of patients and for research, and authorized the appropriation of $15 million for each fiscal year from FY2007 through FY2010. The act reauthorized the national bone marrow registry, authorizing the appropriation of $34 million for FY2006 and $38 million for each year from FY2007 through FY2010. In addition, the act created a database to enable health care workers to search for cord blood and bone marrow matches and linked all these functions under a new name, the C.W. Bill Young Cell Transplantation program.

Legislation enacted in the 111th Congress (P.L. 111-264) authorizes a total of $53 million each year through FY2015 for the C.W. Bill Young Cell Transplantation Program. The law required the Government Accountability Office (GAO) to report, within one year of enactment, on efforts to increase cord blood unit donation and collection for the National Cord Blood Inventory (NCBI). The October 2011 GAO report found that while several practices may increase the number and diversity of cord blood units banked, there were also reported challenges to increasing collection, including resource limitations, competition from other banks that collect units only for the use of family members of the donor, and slowing growth in the demand for cord blood.[30]

Potential Applications of Stem Cell Research

Stem cells provide the opportunity to study the growth and differentiation of individual cells into tissues.[31] Understanding these processes could provide insights into the causes of birth defects, genetic abnormalities, and other disease states. If normal development were better understood, it might be possible to prevent or correct some of these conditions. Stem cells could be used to produce large amounts of one cell type to test new drugs for effectiveness and chemicals for toxicity.[32] The damaging side effects of medical treatments might be repaired with stem cell treatment. For example, cancer chemotherapy destroys immune cells in patients, decreasing their ability to fight off a broad range of diseases; correcting this adverse effect would be a major advance. Stem cells might be transplanted into the body to treat disease (e.g., diabetes, Parkinson's disease) or injury (e.g., spinal cord).[33]

[30] U.S. Government Accountability Office, *National Cord Blood Inventory: Practices for increasing availability for transplants and related challenges*, GAO-12-23, October 2011, http://gao.gov/products/GAO-12-23.

[31] Konrad Hochedlinger, "Your Inner Healers," *Scientific American*, May 2010, pp. 47-53; and, National Institutes of Health, *Regenerative Medicine*, 2006, pp. 3-4, http://stemcells.nih.gov/info/2006report/2006Chapter1.htm. For more information on stem cell biology, see http://stemcells.nih.gov/info/2006report/.

[32] *Regenerative Medicine*, p. 3-4, "Your Inner Healers," p. 53-53.

[33] Ibid.

Before stem cells can be applied to human medical problems, substantial advances in basic cell biology and clinical technique would be required. In addition, very challenging regulatory decisions would be required on any individually created tissue-based therapies resulting from stem cell research that would need individual approval. Such decisions would likely be made by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). The potential benefits would be likely only after many more years of research. Technical hurdles include developing the ability to control the differentiation of stem cells into a desired cell type (like a heart or nerve cell) and to ensure that uncontrolled development, such as cancer, does not occur with some stray cells. Experiments may involve the creation of a chimera, an organism that contains two or more genetically distinct cell types, from the same species or different species.[34] If stem cells are to be used for transplantation, the problem of immune rejection must also be overcome. Some scientists think that the creation of many more embryonic stem cell lines will eventually account for all the various immunological types needed for use in tissue transplantation therapy. Others envision the eventual development of a "universal donor" type of stem cell tissue, analogous to a universal blood donor.

However, if the method used to create iPS cells or if the SCNT technique was employed (using a cell nucleus from the patient), the stem cells created via these methods would be genetically identical to the patient, would presumably be recognized by the patient's immune system, and thus might avoid any tissue rejection problems that could occur in other stem cell therapeutic approaches.[35] Because of this, scientists believe that these techniques may provide the best hope of eventually treating patients using stem cells for tissue transplantation.

Regulation of Research

A Brief History of Federal Policy on Human Embryo Research

Federal funding of *any* type of research involving human embryos, starting with *in vitro* fertilization (IVF) then later the creation of stem cell lines from embryos, had been prohibited by various policy decisions dating back to the late 1970s. This section presents a brief history of federal policy on human embryo research, from the creation of the Ethics Advisory Board during the Carter Administration, the implementation of the Dickey Amendment during the Clinton Administration, and through the human embryonic stem cell policies of the George W. Bush and the Barack Obama Administrations.

The Ethics Advisory Board

The Ethics Advisory Board (EAB) was created in 1978 by the Department of Health, Education and Welfare (HEW), the forerunner of HHS. The EAB was formed at the recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral

[34] Chimeras have been created by scientists in a variety of different ways and have been the subject of research studies for many years. Human chimeras occur naturally when two eggs become fertilized and, instead of developing into twins, they fuse in the uterus creating a single embryo with two distinct sets of genes. For one example, see Constance Holden, "Chimera on a Bike?" *Science*, June 24, 2005, p. 1864.

[35] *Regenerative Medicine*, p. 5, "Your Inner Healers," pp. 52-53.

Research.[36] The National Commission operated from 1974 to 1978 and issued 10 reports, many of which formed the basis of federal regulations for research involving human subjects.[37]

In May 1978 the EAB agreed to review a research proposal involving IVF that had been received by HEW in 1977 and had been approved for its scientific merit. The July 1978 birth in England of the first IVF baby, Louise Brown, aroused great public interest. As a result, HEW in September 1978 "asked the Board to broaden its consideration of the pending application to include the scientific, ethical, legal, and social issues surrounding human IVF and embryo transfer in general."[38] The EAB released its report on May 4, 1979, which found that IVF research was acceptable from an ethical standpoint and could be supported with federal funds.

At that time, federal regulations that govern human subject research stipulated that federally supported research involving human IVF must be reviewed by an EAB.[39] "No action was ever taken by the Secretary with respect to the board's report; for other reasons, the Department dissolved the EAB in 1980. Because it failed to appoint another EAB to consider additional research proposals, HEW effectively forestalled any attempts to support IVF, and no experimentation involving human embryos was ever funded pursuant to the conditions set forth in the May 1979 report or through any further EAB review."[40]

Other types of embryo research ensuing from the development and use of IVF, such as cloning and stem cells, were also blocked from receiving federal support. Enactment of the National Institutes of Health (NIH) Revitalization Act of 1993, P.L. 103-43, Section 121(c), nullified the regulatory provision requiring EAB review of IVF proposals, "removing an 18-year barrier to such research."[41] Congressional intent of Section 121(c) can be found in the report language that accompanied the House bill:

> Subsection (c) nullifies the de facto moratorium currently in place on federal support for research on human in vitro fertilization, a promising area of research on the treatment of infertility. Since 1979, this research has been effectively banned by HHS under regulations which require the approval of such research by an Ethics Advisory Board. Because no such Board has been appointed by the Secretary …, no review of any application for in vitro fertilization has been allowed to go forward at NIH. The effect of this de facto moratorium has been to hobble this area of research, relying only on the private sector without regulation or clear ethical or medical guidelines.[42]

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[36] The National Biomedical Research Fellowship, Traineeship, and Training Act (P.L. 93-348), signed into law on July 12, 1974, required the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to study a wide range of research issues. The National Commission, in its report entitled *Research on the Fetus*, recommended the creation of a national ethical review body. http://bioethics.georgetown.edu/pcbe/reports/past_commissions/research_fetus.pdf. P.L. 93-348 also recommended that HEW establish a program to provide clarification and guidance on ethical issues raised in connection with biomedical research.

[37] 45 C.F.R. Part 46

[38] Ethics Advisory Board, *HEW Support of Research Involving Human In Vitro Fertilization and Embryo Transfer*, Department of Health, Education, and Welfare, May 4, 1979.

[39] 45 C.F.R. §46.204(d) The regulations stated that "no application or proposal involving human *in vitro* fertilization may be funded by the Department [until it] has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint." The regulations were promulgated at a time when IVF was still an experimental technique.

[40] National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research*, Rockville, MD, September 1999, p. 34.

[41] National Institutes of Health, *Report of the Human Embryo Research Panel*, Volume I, September 1994, p. 1.

[42] U.S. Congress, House Committee on Energy and Commerce, *National Institutes of Health Revitalization Act of 1993*, report to accompany H.R. 4, 103rd Cong., 1st sess., March 9, 1993, H. Rept. 103-28 (Washington: GPO, 1993), p. 80.

NIH Human Embryo Research Panel

In response to the NIH Revitalization Act of 1993 (P.L. 103-43, Section 121(c)), the NIH established the Human Embryo Research Panel in 1994 to assess the moral and ethical issues raised by this research and to develop recommendations for NIH review and conduct of human embryo research. The NIH Panel released a report providing guidelines and recommendations on human embryo research in September 1994.[43] The panel identified areas of human embryo research it considered to be unacceptable, or to warrant additional review. It determined that certain types of cloning[44] without transfer to the uterus warranted additional review before the panel could recommend whether the research should be federally funded. However, the panel concluded that federal funding for such cloning techniques followed by transfer to the uterus should be unacceptable into the foreseeable future. The NIH Panel recommended that some areas of human embryo research should be considered for federal funding, including SCNT, stem cells and, under certain limited conditions, *embryos created solely for the purpose of research*.[45] The panel's report was unanimously accepted by the NIH Advisory Committee to the Director (ACD) on December 2, 1994.

After the ACD meeting on December 2, 1994, President William J. Clinton directed NIH *not* to allocate resources to support the "*creation of human embryos for research purposes*." The President's directive did not apply to research involving so-called "spare" embryos, those that sometimes remain from clinical IVF procedures performed to assist infertile couples to become parents. Nor did it apply to human parthenotes, eggs that begin development through artificial activation, not through fertilization. Following the Clinton December 2, 1994, directive to NIH, the agency proceeded with plans to develop guidelines to support research using spare embryos. NIH plans to develop guidelines on embryo research were halted on January 26, 1996, with the enactment of P.L. 104-99, an appropriations law that contained a rider affecting FY1996 funding for NIH. The rider, often referred to as the Dickey Amendment, prohibited HHS from using appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed.

The Dickey Amendment

Private or other non-federal funding for experiments involving embryos has been necessary because Congress attached the Dickey Amendment to legislation that affected FY1996 NIH funding.[46] The amendment, originally introduced by Representative Jay Dickey, prohibits HHS from using appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed.

The Dickey Amendment language has been added to each of the annual Labor, HHS, and Education appropriations acts for FY1997 through FY2012.[47] HHS funding for FY2013 through

[43] National Institutes of Health, *Report of the Human Embryo Research Panel*, Volume I, September 1994, pp. 83.

[44] These were *blastomere separation*, where a two- to eight-cell embryo is treated causing the cells (blastomeres) to separate, and *blastocyst division*, in which an embryo at the more advanced blastocyst stage is split into two.

[45] National Institutes of Health, *Report of the Human Embryo Research Panel*, September 27, 1994.

[46] The original rider can be found in Section 128 of P.L. 104-99; it affected NIH funding for FY1996 contained in P.L. 104-91.

[47] The rider language has not changed significantly from year to year (however there was a technical correction in P.L. 109-149). The rider is found in Title V, General Provisions, of the Labor, HHS and Education appropriations acts in the following public laws: FY1997, P.L. 104-208; FY1998, P.L. 105-78; FY1999, P.L. 105-277; FY2000, P.L. 106-113; FY2001, P.L. 106-554; FY2002, P.L. 107-116; FY2003, P.L. 108-7; FY2004, P.L. 108-199; FY2005, P.L. 108-447;

March 27, 2013, is provided in the Continuing Appropriations Resolution, 2013 (P.L. 112-175) under the same terms and conditions as the FY2012 appropriations act. The Dickey Amendment is found in Section 508 of Division F—Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2012, of P.L. 112-74. It states that

> (a) None of the funds made available in this Act may be used for—
>
> (1) the creation of a human embryo or embryos for research purposes; or
>
> (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).
>
> (b) For purposes of this section, the term 'human embryo or embryos' includes any organism, not protected as a human subject under 45 CFR 46 [the Human Subject Protection regulations] as of the date of enactment of this Act, that is derived by fertilization, parthenogenesis [development from an egg without fertilization], cloning, or any other means from one or more human gametes [sperm or egg] or human diploid cells [cells that have two sets of chromosomes, such as somatic cells].

In addition, no federal funds had been used to support research on stem cells derived from either human embryos or fetal tissue prior to the August 2001 Bush Administration decision (see the "George W. Bush Administration Stem Cell Policy" section).[48] The research published in November 1998 that announced the successful isolation of human embryonic stem cells, performed at the University of Wisconsin and Johns Hopkins University, was supported by private funding from the Geron Corporation.

Clinton Administration Stem Cell Policy

Following the November 1998 announcement on the derivation of human embryonic stem cells by scientists at the University of Wisconsin and Johns Hopkins University, NIH requested a legal opinion from HHS on whether federal funds could be used to support research on human stem cells derived from embryos. The January 15, 1999, response from HHS General Counsel Harriet Rabb found that the Dickey Amendment would not apply to research using human stem cells "because such cells are not a human embryo within the statutory definition." The finding was based, in part, on the determination by HHS that the statutory ban on human embryo research defines an embryo as an *organism* that when implanted in the uterus is capable of becoming a human being. Human stem cells, HHS said, are not and cannot develop into an organism; they lack the capacity to become organisms even if they are transferred to a uterus. As a result, HHS maintained that NIH could support research that uses stem cells derived through private funds, but could not support research that itself, with federal funds, derives stem cells from embryos because of the federal ban in the Dickey Amendment.

Shortly after the opinion by the HHS General Counsel was released, NIH disclosed that the agency planned to fund research on stem cells derived from human embryos once appropriate guidelines were developed and an oversight committee established. NIH Director Harold Varmus appointed a working group that began drafting guidelines in April 1999. Draft guidelines were

FY2006, P.L. 109-149; FY2007, P.L. 110-5; FY2008, P.L. 110-161; FY2009, P.L. 111-8; FY2010, P.L. 111-117; FY2011, P.L. 112-10; FY2012, P.L. 112-74. FY2007 and FY2011 appropriations were provided in full year continuing resolutions (rather than in regular appropriations laws), which maintained the previous year's limitations and restrictions such as the Dickey amendment.

[48] However, federal funds have been provided for research on both human and animal adult stem cells and animal embryonic stem cells.

published in the *Federal Register* on December 2, 1999. About 50,000 comments were received during the public comment period, which ended February 22, 2000. On August 25, 2000, NIH published in the *Federal Register* final guidelines on the support of human embryonic stem cell research. The August 2000 guidelines stated that studies utilizing "stem cells derived from human embryos may be conducted using NIH funds only if the cells were derived (without federal funds) from human embryos that were created for the purposes of fertility treatment and were in excess of the clinical need of the individuals seeking such treatment." Under the August 2000 guidelines, NIH would not fund research directly involving the derivation of human stem cells from embryos; this was prohibited by the Dickey Amendment.

Other areas of research ineligible for NIH funding under the August 2000 guidelines include (1) research in which human stem cells are utilized to create or contribute to a human embryo; (2) research in which human stem cells are combined with an animal embryo; (3) research in which human stem cells are used for reproductive cloning of a human; (4) research in which human stem cells are *derived* using somatic cell nuclear transfer (i.e., the transfer of a human somatic cell nucleus into a human or animal egg); (5) research *utilizing* human stem cells that were derived using somatic cell nuclear transfer; and (6) research utilizing stem cells that were derived from human embryos created for research purposes, rather than for infertility treatment.

NIH began accepting grant applications for research projects utilizing human stem cells immediately following publication of the August 2000 guidelines; the deadline for submitting a grant application was March 15, 2001. All such applications were to be reviewed by the NIH Human Pluripotent Stem Cell Review Group (HPSCRG), which was established to ensure compliance with the August 2000 guidelines. James Kushner, director of the University of Utah General Clinical Research Center, served briefly as chair of the HPSCRG. Applications would also have undergone the normal NIH peer-review process.[49]

The first meeting of the HPSCRG was scheduled for April 25, 2001, to determine whether researchers had followed the August 2000 guidelines in deriving the human embryonic stem cell lines. However, in mid-April 2001, HHS postponed the meeting until a review of the Clinton Administration's policy decisions on stem cell research was completed by the new administration following the election of George W. Bush.[50] According to media sources, the 12 HPSCRG members, whose names were not made public, represented a wide range of scientific, ethical and theological expertise and opinion, as well as at least one "mainstream Catholic."[51]

The Bush Administration conducted a legal review of the Clinton Administration policy decisions on federal support for stem cell research, as well as a scientific review, prepared by NIH, of the status of the research and its applications. The scientific review was released on July 18, 2001, at a hearing held by the Senate Appropriations Subcommittee on Labor, Health and Human Services

[49] According to media sources, as of April 2001 only three grant applications had been submitted to NIH, and one was subsequently withdrawn. (*Washington FAX*, April 19, 2001.) Presumably, scientists were reluctant to invest the time and effort into preparing the necessary paperwork for the NIH grant application process when the prospects of receiving federal funding were uncertain under the new Bush Administration. (P. Recer, "Stem Cell Studies Said Hurt by Doubt," *AP Online*, May 2, 2001.) In a related development, one of the leading U.S. researchers on stem cells, Roger Pederson of the University of California, San Francisco, decided to move his laboratory to the United Kingdom for "the possibility of carrying out my research with human embryonic stem cells with public support." (Aaron Zitner, "Uncertainty Is Thwarting Stem Cell Researchers," *Los Angeles Times*, July 16, 2001, pp. A1, A8.) Human embryonic stem cell research was approved overwhelmingly by the House of Commons in December 2000 and the House of Lords in January 2001.

[50] Rick Weiss, "Bush Administration Order Halts Stem Cell Meeting; NIH Planned Session to Review Fund Requests," *Washington Post*, April 21, 2001, p. A2.

[51] Ibid.

and Education.[52] The NIH report did not make any recommendations, but argued that both embryonic and adult stem cell research should be pursued.

George W. Bush Administration Stem Cell Policy

On August 9, 2001, President George W. Bush announced that for the first time federal funds would be used to support research on human embryonic stem cells, but funding would be limited to "existing stem cell lines where the life and death decision has already been made."[53] President Bush stated that the decision "allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line, by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life." He also stated that the federal government would continue to support research involving stem cells from other sources, such as adult tissues, "which do not involve the same moral dilemma."

Under the Bush policy, federal funds could only be used for research on existing stem cell lines that were derived (1) with the informed consent of the donors, (2) from excess embryos created solely for reproductive purposes, and (3) without any financial inducements to the donors.[54] NIH examined the derivation of all existing stem cell lines and created a registry of lines that satisfied the Bush criteria. According to the White House, this would ensure that federal funds were used to support only stem cell research that is scientifically sound, legal, and ethical. Federal funds would not be used for (1) the derivation or use of stem cell lines derived from newly destroyed embryos, (2) the creation of any human embryos for research purposes, or (3) the cloning of human embryos for any purpose.

NIH created a Human Embryonic Stem Cell Registry listing the cell lines that met the eligibility criteria. The Bush policy and the NIH registry effectively replaced the August 2000 stem cell guidelines that were developed under the Clinton Administration and never fully implemented. Grant proposals for embryonic stem cell research underwent the normal peer-review process without the added review of the HPSCRG, as had been specified under the August 2000 stem cell guidelines. In February 2002, NIH announced the approval of the first expenditures for research on human embryonic stem cells.

The NIH registry originally listed 78 human embryonic stem cell lines as eligible for use in federally funded research under the Bush policy. However, many of these stem cell lines were found to be either unavailable or unsuitable for research.[55] Over time, a growing number of scientists, disease advocates and others became concerned that federally supported research on human embryonic stem cells was limited to 21 cell lines. Because these pre-August 2001 cell lines were developed using 1990s techniques, they were harder to work with and were genetically unstable compared to newer stem cell lines. In reaction to the limitations imposed by the Bush policy, several U.S. research groups decided to develop additional human embryonic stem cell lines using private funding or funds provided by state governments. [56]

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[52] National Institutes of Health, Department of Health and Human Services. *Stem Cells: Scientific Progress and Future Research Directions*, June 2001. The NIH scientific report can be found at http://stemcells.nih.gov/info/scireport/.

[53] The August 9, 2001, *Remarks by the President on Stem Cell Research* can be found http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-2.html

[54] The White House, *Fact Sheet on Embryonic Stem Cell Research*, August 9, 2001, at http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-1.html

[55] In 2009, the NIH registry listed a total of 21 stem cell lines available from six sources. See http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp.

[56] A worldwide survey of laboratories found that as of May 23, 2004, 128 human embryonic stem cell lines had been

States responded to the Bush policy with initiatives to encourage or provide funding for stem cell research to prevent the relocation of scientists and biotechnology firms to other states or overseas. However, without the central direction and coordinated research approach that the federal government provides, others became concerned that the states' actions would result in duplication of research efforts, a lack of oversight for ethical concerns, and ultimately a loss of U.S. preeminence in this important area of basic research. Moreover, research groups studying human embryonic stem cell lines derived after August 2001were required to build new but duplicative laboratories, using funds that could have been spent on associated research, to ensure that absolutely no federal funds were used to support work on the newer stem cell lines.

In April 2004, over 200 House Members sent a letter to President George W. Bush requesting that the Administration revise the stem cell policy and utilize the excess embryos that are created during infertility treatment. The letter pointed out that an estimated 400,000 frozen IVF embryos[57] "will likely be destroyed if not donated, with informed consent of the couple, for research." According to the letter, "scientists are reporting that it is increasingly difficult to attract new scientists to this area of research because of concerns that funding restrictions will keep this research from being successful." The letter went on to state that "[w]e have already seen researchers move to countries like the United Kingdom, which have more supportive policies. In addition, leadership in this area of research has shifted to the United Kingdom, which sees this scientific area as the cornerstone of its biotech industry."

In response, then NIH Director Elias A. Zerhouni wrote "And although it is fair to say that from a purely scientific perspective more cell lines may well speed some areas of human embryonic stem cell research, the president's position is still predicated on his belief that taxpayer funds should not sanction or encourage further destruction of human embryos that have at least the potential for life."[58] Some observers in 2004 believed this indicated a possible policy shift by conceding that science could benefit from additional stem cell lines and the president's position rested solely on ethical arguments.[59] A June 4, 2004, letter signed by 58 Senators also urged President Bush to expand the federal stem cell policy, stating that "despite the fact that U.S. scientists were the first to derive human embryonic stem cells, leadership in this area of research is shifting to other countries such as the United Kingdom, Singapore, South Korea and Australia."

On July 14, 2004, HHS announced that NIH would establish Centers of Excellence in Translational Stem Cell Research and a National Embryonic Stem Cell Bank.[60] Then-Secretary Tommy Thompson stated that "before anyone can successfully argue the stem cell policy should be broadened, we must first exhaust the potential of the stem cell lines made available with the

created since August 9, 2001; all were ineligible for use in federally funded research under the Bush policy. Gareth Cook, "94 New Cell Lines Created Abroad since Bush Decision," *Boston Globe*, May 23, 2004, p. A14. Another survey found that as of January 1, 2006, 414 human embryonic stem cell lines had been created in at least 20 countries. Anke Guhr et al., "Current State of Human Embryonic Stem Cell Research: An Overview of Cell Lines and Their Use in Experimental Work," *Stem Cells 2006*, v. 24, p. 2187-2191, at http://www.StemCells.com.

[57] A survey conducted in 2002 and published in 2003 by the Society for Assisted Reproductive Technology and RAND determined that nearly 400,000 frozen embryos are stored in the United States, but most are currently targeted for patient use. See David I. Hoffman et al., "Cryopreserved Embryos in the United States and Their Availability for Research," *Fertility and Sterility*, vol. 79, May 2003, pp. 1063-1069.

[58] Letter from Elias A. Zerhouni, Director, National Institutes of Health, to The Honorable Diana DeGette and The Honorable Michael Castle, May 14, 2004.

[59] Rick Weiss, "Bush's Stem Cell Policy Reiterated, but Some See Shift," *The Washington Post*, May 16, 2004, p. A18.

[60] Andrew J. Hawkins, "NIH Stem Cell Bank, Centers of Excellence Will Fast-Track Translational Research, Says Thompson," *Washington FAX*, July 15, 2004.

policy."[61] In reaction, the President of the Coalition for the Advancement of Medical Research stated that "creating a bank to house stem cell lines created before August 2001 does nothing to increase the wholly inadequate supply of stem cell lines for research."[62]

At a March 2007 Senate hearing, then NIH Director Zerhouni stated, in response to a question on the status of stem cell research, "It's not possible for me to see how we can continue the momentum of science and research with the stem cell lines we have at NIH that can be funded."[63] When asked about research alternatives, Zerhouni stated that "the presentations about adult stem cells holding as much or more potential than embryonic stem cells, in my view, do not hold scientific water. I think they are overstated."[64] He noted that overseas competitors were investing heavily in human embryonic stem cell research. "I think it is important for us not to fight with one hand tied behind our back here.… I think it's time to move forward on this area. It's time for policy makers to find common ground, to make sure that NIH does not lose its historical leadership.... To sideline NIH on such an issue of importance in my view is shortsighted."[65] These statements were notable at the time because they were divergent with Bush Administration policy.

On June 20, 2007, President Bush signed Executive Order 13435 directing the support of "research on the isolation, derivation, production and testing of stem cells that are capable of producing all or almost all of the cell types of the developing body and may result in improved understanding of or treatments for diseases and other adverse health conditions, but are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus."[66] However, many scientists continued to stress that research should focus on all types of stem cells, including those derived from human embryos.

Obama Administration Stem Cell Policy

On March 9, 2009, President Barack Obama signed Executive Order 13505: "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells." The Obama executive order revoked the Bush presidential statement of August 9, 2001, as well as Executive Order 13435 signed by President Bush on June 20, 2007.[67] The Obama executive order permits the Secretary of HHS through NIH to "support and conduct responsible, scientifically worthy human stem cell

[61] Ibid.

[62] Ibid.

[63] U.S. Congress, Senate Committee on Appropriations, Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, Hearing on H.R. 3043/S. 1710, 110th Cong., 1st sess., March 19, 2007, p. 19.

[64] Ibid., p. 20.

[65] Ibid., p. 21. In May 2008 Zerhouni made similar statements about the need for additional embryonic stem cell lines and the value of pursuing all avenues of stem cells research at a House hearing. U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, *Stem Cell Science: The Foundation for Future Cures*, 110th Cong., 2nd sess., May 8, 2008, H. Hrg 110-115 (Washington: GPO, 2008), pp. 139.

[66] The White House, Office of the Press Secretary, "Executive Order: Expanding Approved Stem Cell Lines in Ethically Responsible Ways," June 20, 2007, at http://georgewbush-whitehouse.archives.gov/news/releases/2007/06/20070620-6.html

[67] "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," March 9, 2009, at http://www.whitehouse.gov/the_press_office/Removing-Barriers-to-Responsible-Scientific-Research-Involving-Human-Stem-Cells/. On the same day, President Obama issued a memorandum on scientific integrity directing the head of the White House Office of Science and Technology Policy "to develop a strategy for restoring scientific integrity to government decision making." The White House, Office of the Press Secretary, Remarks of President Barack Obama-As Prepared for Delivery, Signing of Stem Cell Executive Order and Scientific Integrity Presidential Memorandum, March 9, 2009, at http://www.whitehouse.gov/the_press_office/Remarks-of-the-President-As-Prepared-for-Delivery-Signing-of-Stem-Cell-Executive-Order-and-Scientific-Integrity-Presidential-Memorandum/.

research, including human embryonic stem cell research, to the extent permitted by law" and directed NIH to review existing guidelines and "issue new NIH guidance on such research" within 120 days of the date of the executive order (see "NIH Stem Cell Guidelines and Funding for Stem Cell Research"). The Obama decision allows scientists to use federal funds for research utilizing the hundreds of human embryonic stem cell lines that have been created since the Bush 2001 policy.

To ensure that all federally funded human stem cell research is conducted according to the same principles as the new NIH guidelines, a July 30, 2009, presidential memorandum directed the heads of all executive departments and agencies that support and conduct stem cell research to adopt the guidelines.[68]

Shortly after the 2009 guidelines were issued, opponents of human embryonic stem cell research brought suit in federal court arguing that federal funding of such research was barred by the Dickey amendment's prohibition against federal funding of "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero* [under federal law]."[69] Specifically, the litigation turned on whether HHS could lawfully interpret the term "research" to include only activities performed once human embryonic stem cells had been isolated, or whether "research" must also include the antecedent embryonic stem cell derivation activities that generally resulted in the destruction of human embryos. Although federal funding of embryonic stem cell research was briefly enjoined by a preliminary injunction between August 23 and September 9, 2010,[70] the United States Court of Appeals for the D.C. Circuit ultimately held that the text and legislative history of the Dickey amendment sufficiently supported HHS's narrower construction of the term "research" and allowed federal funding of human embryonic stem cell research to continue under the 2009 guidelines.[71] On January 7, 2013, the Supreme Court denied the plaintiffs' petition for review and let the D.C. Circuit's opinion stand.[72]

The Obama policy eliminates the need to separate federally funded research from research conducted with state or private funds on cell lines that were previously ineligible for federal funding under the Bush policy; this often required building new but duplicative laboratories under the Bush policy using funds that could have been spent on associated research. States, such as California, Connecticut, Illinois, Maryland, New Jersey, and New York, may be reconsidering

[68] The Office of the President, "Guidelines for Human Stem Cell Research: Memorandum for the Heads of Executive Departments and Agencies," 74 *Federal Register* 38885-38886, August 5, 2009.

[69] The suit had initially been dismissed for lack of standing. Sherley v. Sebelius, 686 F. Supp. 2d 1 (D.D.C. 2009). However, the case was reinstated after an appellate court ruled that two adult stem cell researchers had sufficiently alleged that they would suffer increased competition for NIH grants if more embryonic stem cell lines were made eligible for federal funds. Sherley v. Sebelius, 610 F.3d 69 (D.C. Cir. 2010).

[70] Sherley v. Sebelius, Civ. No. 1:09-cv-1575 RCL (D.D.C. August 23, 2010) (granting preliminary injunction barring HHS from "implementing, applying, or taking any action whatsoever pursuant to" the NIH 2009 Guidelines "or otherwise funding research involving human embryonic stem cells as contemplated in the Guidelines"); Sherley v. Sebelius, No. 10-5287 (D.C. Cir. September 9, 2010) (granting emergency administrative stay of preliminary injunction).

[71] Sherley v. Sebelius, 644 F.3d 388 (D.C. Cir. 2011) (vacating preliminary injunction). Following the D.C. Circuit's decision, the district court also dismissed the plaintiffs' alternative claim which argued that providing federal funding for human embryonic stem cell research encouraged the derivation of new embryonic stem cells, thereby subjecting human embryos to an increased risk of destruction. Sherley v. Sebelius, 776 F. Supp. 2d 1 (D.D.C. 2011) *aff'd*, 689 F.3d 776 (D.C. Cir. 2012), *cert. denied* 81 U.S.L.W. 3221 (2013).

[72] Sherley v. Sebelius, 81 U.S.L.W. 3221 (2013).

their funding of stem cell research given the change in federal policy that occurred under the Obama Administration and the impact of the nation's economic recession on state budgets.

NIH Stem Cell Guidelines and Funding for Stem Cell Research

On April 17, 2009, NIH announced the release of draft guidelines for the support and conduct of "ethically responsible and scientifically worthy" human stem cell research, including human embryonic stem cell research. The draft guidelines were published in the *Federal Register* on April 23, 2009.[73] Written comments on the draft guidelines were accepted by NIH through May 26, 2009. About 49,000 comments were received by the agency. Final guidelines were issued by NIH on July 6, 2009, and became effective on July 7, 2009.[74] The 2009 NIH guidelines specify the conditions that must be met and supported with documentation before a human embryonic stem cell line could be used in research conducted with federal funds; these conditions are repeated below.

The human embryonic stem cells should have been derived from human embryos

- that were created using IVF for reproductive purposes and were no longer needed for that purpose;
- that were donated by individuals who sought reproductive treatment and who gave voluntary written consent for the human embryos to be used for research purposes;
- for which all of the following can be assured and documentation provided, such as consent forms, written policies, or other documentation provided:
    - All options available in the health care facility where treatment was sought pertaining to the embryos no longer needed for reproductive purposes were explained to the individual(s) who sought reproductive treatment.
    - No payments, cash or in kind, were offered for the donated embryos.
    - Policies and/or procedures were in place at the health care facility where the embryos were donated that neither consenting nor refusing to donate embryos for research would affect the quality of care provided to potential donor(s).
    - There was a clear separation between the prospective donor(s)'s decision to create human embryos for reproductive purposes and the prospective donor(s)'s decision to donate human embryos for research purposes. Specifically (1) Decisions related to the creation of human embryos for reproductive purposes should have been made free from the influence of researchers proposing to derive or utilize human embryonic stem cells in research. The attending physician responsible for reproductive clinical care and the researcher deriving and/or proposing to utilize human embryonic stem cells should not have been the same person unless separation was not practicable. (2) At the time of donation, consent for that donation should have been obtained from the individual(s) who had sought reproductive treatment. That is, even if potential donor(s) had given prior indication of

[73] Department of Health and Human Services, National Institutes of Health, "Draft National Institutes of Health Guidelines for Human Stem Cell Research Notice," 74 *Federal Register* 18578-18580, April 23, 2009.

[74] Department of Health and Human Services, National Institutes of Health, "National Institutes of Health Guidelines for Human Stem Cell Research," 74 *Federal Register* 32170-32175, July 7, 2009.

their intent to donate to research any embryos that remained after reproductive treatment, consent for the donation for research purposes should have been given at the time of the donation. (3) Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.

- During the consent process, the donor(s) were informed of the following: (1) the embryos would be used to derive human embryonic stem cells for research; (2) what would happen to the embryos in the derivation of human embryonic stem cells for research; (3) the human embryonic stem cells derived from the embryos might be kept for many years; (4) the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefits from the use of the human embryonic stem cells, such as who may be recipients of cell transplants; (5) the research is not intended to provide direct medical benefit to the donors; (6) the results of research using the human embryonic stem cells may have commercial potential, and the donor(s) would not receive financial or any other benefits from any such commercial development; (7) whether information that could identify the donor(s) would be available to researchers.

Under the 2009 NIH guidelines, funding would not be allowed for research using human embryonic stem cells derived from other sources, including SCNT, parthenogenesis (development from an egg without fertilization), or IVF embryos created for research purposes. At a news conference on April 17, 2009, the Acting Director of NIH, Raynard Kington, stated that there is "strong broad support for the use of federal funds to conduct human embryonic stem cell research on cell lines derived from embryos created for reproductive purposes," and pointed to legislation twice passed by Congress as evidence.[75] Dr. Kington stated that "there is not similar broad support for using the other sources" and that NIH is not aware of any human stem cell lines created via SCNT or "from embryos created specifically for research purposes."[76] A survey of the scientific literature conducted by a researcher at Harvard University found at least 783 cell lines created from excess IVF embryos and did not find "a report that IVF was used specifically to make a line of human embryonic stem cells."[77]

Some were concerned that the lines that were eligible for use in federally funded research under the 2001 Bush policy may not qualify under the 2009 NIH guidelines because of the very detailed requirements for informed consent which were not in place and widely observed prior to 2006.[78] It was suggested that it may be necessary to "grandfather" some of these older cell lines to allow for their continued use in research.[79] Rather than grandfathering, the 2009 NIH guidelines allow a Working Group of the Advisory Committee to the Director to review the ethical principles and

[75] National Institutes of Health Officials Hold News Teleconference on Federal Stem Cell Research Funding Guidelines, CQ Newsmaker Transcripts, April 17, 2009.

[76] Ibid.

[77] Constance Holden, "For Congress and NIH, Headaches Ahead on Stem Cells," *Science*, vol. 323 (March 20, 2009), pp. 1552-1553.

[78] Constance Holden and Jocelyn Kaiser, "Draft Stem Cell Guidelines Please Many, Disappoint Some," *Science*, vol. 324 (April 24, 2009), p. 446.

[79] Ibid.

procedures used in the process of obtaining informed consent for the donation of the embryo and advise NIH on whether the cell line should be eligible for NIH funding.

In December 2009, the agency created a new NIH registry of human embryonic stem cell lines that are eligible for use in research supported by federal funds. In February 2010, the agency proposed expanding the definition of what constitutes a human embryonic stem cell to include "early stage embryos up to and including" the blastocyst stage.[80] The previous definition, "cells that are derived from the inner cell mass of blastocysts," excluded certain human embryonic stem cell lines which might be otherwise appropriate for federal funding. In April 2010 NIH approved four stem cell lines developed by the WiCell Research Institute that had been eligible for federal funding under the Bush policy. The H9 stem cell line had been widely used by stem cell researchers. As of January 8, 2013, a total of 200 stem cell lines are listed in the registry.[81]

As discussed above, federal funding of human embryonic stem cell research were briefly enjoined between August 23 and September 9, 2010.[82] During this time, NIH placed a notice on its website that suspended action on grant applications and contracts that involve human embryonic stem cells and other matters related to the 2009 NIH guidelines.[83] NIH stated that "grant awards that were funded on or before August 23, 2010, are not affected by the preliminary injunction order, and award recipients may continue to expend the funds awarded to them prior to the date of the injunction."[84] On August 30, 2010, the agency ordered that all intramural researchers using human embryonic stem cells must stop their experiments immediately.[85] Eight research projects were affected, most if not all used cell lines that were approved under the Bush policy.[86]

In a statement on the agency's website, NIH Director Francis S. Collins said, "The recent court ruling that halted the federal funding of human embryonic stem cell research could cause irreparable damage and delay potential breakthroughs to improve care for people living with serious diseases and conditions such as spinal cord injury, diabetes, or Parkinson's disease. The injunction threatens to stop progress in one of the most encouraging areas of biomedical research, just as scientists are gaining momentum—and squander the investment we have already made."[87] In a joint statement, the Association of American Medical Colleges, the Association of American Universities, the Association of Public and Land-grant Universities, and the Council on Governmental Relations said the court injunction "not only blocks potential life-saving research but also threatens to undermine the system of peer-reviewed science that has helped make America the unquestioned world leader in scientific discovery."[88]

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[80] Department of Health and Human Services, National Institutes of Health, "NIH Guidelines for Human Stem Cell Research," 75 *Federal Register* 8085-8086, February 23, 2010.

[81] See http://grants.nih.gov/stem_cells/registry/current.htm.

[82] See *supra* at "Obama Administration Stem Cell Policy."

[83] NIH, Status of Applications and Awards Involving Human Embryonic Stem Cells, and Submissions of Stem Cell Lines for Eligibility Consideration, available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-126.html.

[84] Ibid.

[85] Jocelyn Kaiser, "NIH orders immediate shutdown of intramural human embryonic stem cell research," *ScienceInsider*, August 30, 2010, http://news.sciencemag.org/scienceinsider/2010/08/nih-orders-immediate-shutdown.html.

[86] Ibid.

[87] NIH Director's Response to Stem Cell Injunction, August 26, 2010, at http://www.nih.gov/about/director/08262010statement_stemcellinjunction.htm.

[88] University and Hospital Associations Respond to Injunction on Funding of Embryonic Stem Cell Research, August 27, 2010, at http://www.aamc.org/newsroom/pressrel/2010/100827.htm.

Once the preliminary injunction was stayed on September 9, 2010, NIH grant review and other activities under the NIH Guidelines were permitted to continue even though the underlying case was still being litigated.[89]

Funding for stem cell research by NIH is shown in **Table 1.** NIH received $10 billion in funds provided by the stimulus package, the American Recovery and Reinvestment Act of 2009 (ARRA, P.L. 111-5); **Table 1** shows the amount of ARRA funds used for research on stem cells. The NIH website provides more information on stem cell activities and funding opportunities.[90]

Table 1. National Institutes of Health Funding on Stem Cell Research

($ in millions)

Stem Cell Research	FY08 Actual	FY09 Actual (non-ARRA)	FY09 Actual (ARRA)	FY10 Actual (non-ARRA)	FY10 Actual (ARRA)	FY11 Actual	FY12 Estimate	FY13 Estimate
Human Embryonic	88	120	23	126	40	123	124	123
Non-Human Embryonic	150	148	29	175	20	165	166	165
Human Non-Embryonic	297	339	58	341	74	395	396	396
Non-Human Non-Embryonic	497	550	88	570	74	620	622	621
Human Cord Blood/Placenta	38	42	9	40	7	36	36	36
Non-Human Cord Blood/Placenta	9	10	1	5	1	10	10	10
Total, Stem Cell Research	**938**	**1,044**	**187**	**1,099**	**187**	**1,179**	**1,185**	**1,182**

Source: NIH website, table published February 13, 2012, accessed on January 8, 2013.

Notes: Amounts in the table reflect the Research, Condition, and Disease Categorization (RCDC) system, a process implemented in 2008. More information on RCDC can be found on the NIH website: http://report.nih.gov/rcdc/categories/.

FDA Regulation of Stem Cell Research

FDA, the agency that ensures the safety and efficacy of food, drugs, medical devices and cosmetics, regulates stem cell research aimed at the development of any "product" subject to its approval. The regulation of cells or tissues intended for implantation or infusion into a human patient is the responsibility of the FDA Center for Biologics Evaluation and Research (CBER). FDA refers to such cells as HCT/Ps, which stands for human cells, tissue, and cellular and tissue-based products. Stem cells (whether derived from embryos, cord blood, adult cells or iPS cells) are just one example of HCT/P. Other examples of HCT/Ps include bone, skin, corneas,

[89] NIH, Amended Status of Applications and Awards Involving Human Embryonic Stem Cells, and Submissions of Stem Cell Lines for Eligibility Consideration, available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-136.html.

[90] See http://stemcells.nih.gov/research/funding/.

ligaments, tendons, dura mater, heart valves, oocytes, and semen. HCT/Ps are regulated under 21 CFR 1271.[91]

The agency's website states that FDA uses a risk-based approach to regulation, focusing on three general areas:

1. limiting the risk of transmission of communicable disease from donors to recipients;
2. establishing manufacturing practices that minimize the risk of contamination;
3. requiring an appropriate demonstration of safety and effectiveness for cells and tissues that present greater risks due to their processing or their use.[92]

Some HCT/Ps are regulated solely under Section 361 of the Public Health Service (PHS) Act, which is concerned with control of communicable diseases. These HCT/Ps must meet the requirements in 21 CFR 1271 but are not required to undergo FDA premarket review (including a license, approval, or clearance). Such HCT/Ps meet all the criteria listed in 21 CFR 1271.10.[93] Establishments that manufacture HCT/Ps that meet the criteria in 1271.10 must register with FDA, submit a list of each HCT/P manufactured, and comply with the requirements of 21 CFR 1271.

There are exceptions from the requirements of 21 CFR 1271; these are listed in 21 CFR 1271.15. Some examples of such exceptions include establishments that use HCT/Ps solely for nonclinical scientific or educational purposes; remove HCT/Ps from an individual and implant such HCT/Ps into the same individual during the same surgical procedure; or recover reproductive cells or tissue and immediately transfer them into a sexually intimate partner of the cell or tissue donor.

HCT/Ps that do not meet the criteria listed in 1271.10 and do not qualify for any of the exceptions listed in 1271.15 are regulated as a drug, device, and/or biological product under the Federal Food, Drug, and Cosmetic Act and/or Section 351 of the PHS Act; all such HCT/Ps would require premarket approval (including a license, approval or clearance).

In January 2009, FDA approved a request to begin tests of human embryonic stem cells in 8 to 10 patients with recent spinal cord injuries. The Phase I clinical trial supported by Geron, a California biotechnology company, was the first to use such cells in human subjects.[94] In November 2011 Geron announced that it would stop work on its stem cell therapy program to

[91] Tissues recovered prior to May 25, 2005, are regulated under 21 CFR 1270. http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/QuestionsaboutTissues/ucm101559.htm.

[92] Ibid.

[93] The criteria in 21 CFR 1271.10 are as follows: the HCT/Ps are minimally manipulated; the manufacture does not involve the combination of the cells with another article (except for water or a sterilizing, preserving, or storage agent); and, are intended for homologous use only. Homologous use is defined as "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a HCP/T that performs the same basic function or functions in the recipient as in the donor." 21 C.F.R. §1271.3. In addition, the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or, the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and it is either for autologous use, or for allogeneic use in a first-degree or second-degree blood relative, or for reproductive use. Autologous use is defined as "the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissues were recovered." 21 C.F.R. §1271.3.

[94] In August 2009, the study was halted before the first patient was enrolled due to safety concerns. In July 2010, Geron announced that FDA allowed the trial to begin. Eligible patients agreed to have stem cells injected into the spinal cord injury site between 7 and 14 days after the injury. The injected cells were intended to help repair the insulation, called myelin, around nerve cells. Geron Corporation, "Geron to Proceed with First Human Clinical Trial of Embryonic Stem Cell-Based Therapy," press release, July 30, 2010.

focus on cancer therapy.[95] The decision was made because of financial problems, forcing Geron to cut 38% of its workforce to save $25 million per year.[96] The company will continue to monitor the four patients who have received stem cell injections but will not enroll new patients. The four patients have not experienced serious adverse events but have also shown no signs that the therapy was reversing the spinal cord injury.

In November 2010, a second U.S. company, Advanced Cell Technology (ACT) headquartered in Santa Monica, CA, announced that it had received approval from FDA to conduct a clinical trial using human embryonic stem cells to treat two conditions which cause blindness.[97] The ACT trial has treated two patients as of November 2011.[98]

Some have expressed concern over the possibility that transplanted stem cells may form a type of tumor called a teratoma. Extensive studies in rodents were performed to assure FDA that the stem cells did not cause tumors in animals.[99]

Stem Cell Research Guidelines by Other Entities

Two non-federal entities have also played a role in providing guidelines for the conduct of stem cell research. Because of the lack of federal regulation of such research during the George W. Bush Administration, the National Academies developed voluntary guidelines for deriving, handling, and using human embryonic stem cells.[100] The International Society for Stem Cell Research (ISSCR), "an independent, nonprofit organization formed in 2002 to foster the exchange of information on stem cell research,"[101] developed guidelines in order to facilitate international collaboration by providing a uniform set of practices for scientists worldwide.

National Academies Guidelines

In July 2004 the National Academies established the committee on Guidelines for Human Embryonic Stem Cell Research to develop voluntary guidelines for deriving, handling and using human embryonic stem cells due to the lack of federal regulation of such research at that time. The National Academies stated that there should be a global ban on human reproductive cloning and therefore the guidelines focused only on therapeutic and research uses of human embryonic stem cells and somatic cell nuclear transfer.

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[95] Monya Baker, "Stem-cell pioneer bows out," *Nature*, vol. 479 (November 24, 2011), p. 459.

[96] Jocelyn Kaiser, "Researchers mull impact of Geron's sudden exit from field," *Science*, vol. 334 (November 25, 2011), p. 1043.

[97] The two eye conditions are Stargardt's macular dystrophy, an inherited eye disease, and dry age-related macular degeneration. "News in Brief: Policy Playback," *Nature Medicine*, vol. 17, no. 1 (January 2011), p. 12.

[98] Jocelyn Kaiser, "Researchers mull impact of Geron's sudden exit from field," *Science*, vol. 334 (November 25, 2011), p. 1043.

[99] Jennifer Couzin, "Celebration and concern over U.S. trial of embryonic stem cells," *Science*, vol. 323 (January 30, 2009), p. 568.

[100] The National Academies bring together committees of experts in all areas of science and technology to address critical national issues and give advice on a pro bono basis to the federal government and the public. The National Academies is comprised of four organizations: the National Academy of Sciences (NAS), established by Abraham Lincoln in 1863; the National Academy of Engineering, established by NAS in 1964; the Institute of Medicine, established by NAS in 1970; and, the National Research Council, established in 1916 by NAS at the request of President Wilson.

[101] See the ISSCR website at http://www.isscr.org/home/about-us.

The committee released its "Guidelines for Human Embryonic Stem Cell Research" on April 26, 2005. The document provided guidance on informed consent of donors and stated that there should be no financial incentives in the solicitation or donation of embryos, sperm, eggs, or somatic cells for research purposes. The guidelines recommended that each institution conducting human embryonic stem cell research establish an oversight committee, including experts in the relevant areas of science, ethics, and law, as well as members of the public, to review all proposed experiments. The guidelines recommended that a national panel be established to oversee the issue in general on a continuing basis.

The Human Embryonic Stem Cell Research Advisory Committee met for the first time in July 2006 and held a number of meetings to gather information about the need to revise the guidelines. In February 2007, a revised version of the guidelines was published with minor changes affecting Sections 1 (Introduction) and Section 2 (Establishment of an Institutional Embryonic Stem Cell Research Oversight Committee).[102] The guidelines were updated again in September 2008 to reflect the advances with iPS cells by including a new section entirely devoted to this area of research.[103]

International Society for Stem Cell Research Guidelines

In February 2007, the International Society for Stem Cell Research (ISSCR) released its "Guidelines for the Conduct of Human Embryonic Stem Cell Research."[104] The ISSCR guidelines were developed by a committee of scientists, ethicists, and legal experts from 14 countries in order to "facilitate international collaboration by encouraging investigators and institutions to adhere to a uniform set of practices."[105] In drafting the guidelines, the ISSCR committee used as a model the National Academies guidelines, the regulations of the California Institute for Regenerative Medicine, and "governmental regulations already in place in other countries, particularly that of the Human Fertilisation and Embryology Authority of the United Kingdom."[106]

In order to ensure the responsible development of safe and effective stem cell therapies for patients, the ISSCR released in December 2008 a second guidance document, "Guidelines for the Clinical Translation of Stem Cells." In addition, due to concerns over unproven stem cell therapies being marketed directly to patients, the ISSCR also developed a handbook to be used by patients and their doctors in evaluating a stem cell therapy.[107] In the press release for the guidelines they noted "[t]oo often rogue clinics around the world exploit patients' hopes by offering unproven stem cell therapies, typically for large sums of money and without credible scientific rationale, oversight or patient protections."[108] According to ISSCR, this concern was substantiated by a study conducted by the University of Alberta, Canada, which analyzed the

[102] The 2007 Amendment to the 2005 Guidelines for Human Embryonic Stem Cell Research can be found at http://www.nap.edu/catalog/11278.html.

[103] The original 2005 Guidelines as well as the 2007 amended version and the 2008 amended version can be found at http://www.nap.edu/catalog.php?record_id=12553.

[104] The ISSCR Guidelines can be found at http://www.isscr.org/docs/default-source/hesc-guidelines/isscrhescguidelines2006.pdf.

[105] George Q. Daley, Lars Ahrlund-Richter, Jonathan M. Auerbach et al., "The ISSCR Guidelines for Human Embryonic Stem Cell Research," *Science*, vol. 315 (February 2, 2007), pp. 603-604.

[106] Ibid.

[107] The ISSCR Guidelines and the Patient Handbook are at http://www.isscr.org/home/publications/ClinTransGuide.

[108] International Society for Stem Cell Research, "The ISSCR Releases New Guidelines to Shape Future of Stem Cell Therapy," press release, December 3, 2008.

claims of 19 Internet sites offering "stem cell therapies," the vast majority of which "over promise results and gravely underestimate the potential risks of their offered treatments."[109]

State Laws that Restrict Stem Cell Research[110]

The National Council of State Legislatures compiled information on state laws that restrict stem cell research. As of January 2008, the most recent summary information available, many states restrict research on aborted fetuses or embryos, but research is often permitted with consent of the parent or parents. Almost half of the states also restrict the sale of fetuses or embryos. Louisiana is the only state that specifically prohibits research on in vitro fertilized (IVF) embryos. Illinois and Michigan also prohibit research on live embryos. Arkansas, Indiana, Michigan, North Dakota, and South Dakota prohibit research on cloned embryos. Virginia may also ban research on cloned embryos, but the statute may leave room for interpretation because human being is not defined. (There may be disagreement about whether human being includes blastocysts, embryos or fetuses.) California, Connecticut, Illinois, Iowa, Massachusetts, New Jersey, New York, and Rhode Island have laws that prohibit cloning for the purpose of initiating a pregnancy, but allow cloning for research.

Several states limit the use of state funds for cloning or stem cell research. Missouri forbids the use of state funds for reproductive cloning but not for cloning for the purpose of stem cell research, and Maryland's statutes prohibit state-funded stem cell researchers from engaging in reproductive cloning. Arizona law prohibits the use of public monies for reproductive or therapeutic cloning. Nebraska statutes limit the use of state funds for embryonic stem cell research. Restrictions only apply to state healthcare cash funds provided by tobacco settlement dollars. State funding available under Illinois Executive Order 6 (2005) may not be used for reproductive cloning or for research on fetuses from induced abortions.

In reaction to the restrictive federal policy for funding research under the George W. Bush Administration, several states (California, Connecticut, Illinois, Indiana, Maryland, Massachusetts, New Jersey, New York, Ohio, Washington, Wisconsin, Virginia) have been encouraging or providing funding for stem cell research (adult, embryonic, and in some cases SCNT as well), in order to remain competitive and prevent the relocation of scientists and biotechnology firms to other states or overseas. The change in federal policy on embryonic stem cell research under the Obama Administration as well as the current economic situation has caused some states to reevaluate their stem cell research efforts.[111]

Legislation

Legislation introduced in the 111th and 112th Congresses would have codified the Obama stem cell policy and prevented reversal by future Administrations.[112] In addition, the legislation would have banned funding for reproductive human cloning, and required that stem cell lines meet ethical

[109] Ibid.

[110] The information in this section was obtained from "State Embryonic and Fetal Research Laws," updated January 2008 on the National Council of State Legislatures website, at http://www.ncsl.org/programs/health/genetics/embfet.htm, visited January 10, 2013.

[111] Constance Holden, "CIRM Close-Hauled, Seeks Bonds to Sustain Headway," *Science*, vol. 323 (March 27, 2009), pp. 1660-1661, and Constance Holden, "Most State Stem Cell Efforts Staying Afloat," vol. 323 (March 27, 2009), pp. 1660-1661.

[112] H.R. 2376 (DeGette), the Stem Cell Research Advancement Act of 2011 and H.R. 4808 (DeGette), the Stem Cell Research Advancement Act of 2009.

guidelines established by the NIH and that the guidelines be reviewed every three years. There was no further action on such legislation during the 111th Congress or the 112th Congress. The table below depicts action during the 109th and 110th Congresses on human embryonic stem cell research legislation.

Action on Human Embryonic Stem Cell Research Legislation (109th and 110th Congresses)

	109th Congress
May 24, 2005	House passed H.R. 810 (Castle), the Stem Cell Research Enhancement Act of 2005, by a vote of 238 to 194.
July 18, 2006	Senate passed H.R. 810 by a vote of 63 to 37.
July 19, 2006	President George W. Bush vetoed H.R. 810, the first veto of his presidency.
July 19, 2006	An attempt in the House to override the veto was unsuccessful.
	110th Congress
January 11, 2007	House passed H.R. 3 (DeGette), the Stem Cell Research Enhancement Act of 2007, by a vote of 253 to 174.[113]
April 11, 2007	Senate passed S. 5 (Reid), Stem Cell Research Enhancement Act of 2007, by a vote of 63 to 34.[114]
June 7, 2007	House passed S. 5 by a vote of 247 to 176.
June 20, 2007	President George W. Bush vetoed S. 5.

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[113] H.R. 3 (DeGette) was identical to the 109th Congress bill H.R. 810 (Castle).

[114] S. 5 was the same as H.R. 3, except it had an additional section supporting research on alternative human pluripotent stem cells.

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